

Review Article



Acne Vulgaris: An Update on Current Therapy and Advances in Treatment Strategies

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ABSTRACT

The era of 21st century marks the era of therapeutic and technological advancements in treatment strategy for various life threatening diseases like Cancer, Diabetes, Alzheimer's etc. to the diseases of skin such as psoriasis, alopecia, warts, eczema, rosacea which are concerned with physical well-being of the individuals. Among such skin diseases, Acne Vulgaris is given special focus as it is most common and wide spread disease among adolescents and the immediate effect of acne are visible as sign of eruption on the face and is thus generally associated with disabling social and psychological effects. Though the currently used medicaments are effective against the disease causing by *P.acne*, the associated side effects of medication is a prominent issue based on the duration of treatment that vary largely based on the severity of the disease. Several new treatment alternatives are thus being researched and practiced for achieving timely treatment and shortening the duration of therapy and minimizing the side effects. This review focuses on providing an understanding of the etiological aspects of the disease and the medicaments that are employed as first line and second line agents in treatment and advances in the technology with some new aspects in Acne Vulgaris treatment. It holds the promise for safeguarding future needs of population that aren't health conscious in refraining the effect of a common commensal bacteria residing in skin microbiome.

Keywords: Acne Vulgaris, Inflammation, *P.acne*, Treatment, Topical, Photodynamic Therapy.

INTRODUCTION

Acne is a multifactorial chronic inflammatory disease with almost average 50% occurrence in the individuals between the age of 20-30 years with the universal spread. Inflammation occurs in the pilosebaceous unit of hair follicles of the skin layer that are associated with an oil gland. The most common acne prone area is the facial part, the back and the chest where sebaceous follicles are most common. Clinically acne lesions are identified by seborrhea (excess oil secretion), non-inflammatory (comedones), inflammatory (papules and pustules) and scars.^{1,2} The epidemiological evidences suggest that the predisposition or the risk of acne development seems to be related to ethnicity, diet, hygiene, smoking, obesity and stress, and each has varied level of impact and significance in manifestation of its symptoms.³ Based on severity, acne is classified as inflammatory and non-inflammatory type. The non-inflammatory lesions represented by obstructive acne consist of closed (macrocomedones or white heads) and open (blackhead) comedones.

Macrocomedones can only identified with microscopy and look like normal skin. Inflammatory acne is more critical and not easy to control because of the involvement of host immune system. It includes papule, pustule, nodular and cystic acne. In this lesion follicular epithelium is damaged and intra-dermal inflammation occurs. If the dermal cell rupture occurs it elicits the intense inflammatory response in the dermis layer. An interesting thing in acne is its spontaneous resolution by

follicular cycling process.⁴ Acne lesions are grades on various scale based on its severity. Some of the severe forms of the disease are nodulocystic acne and acne conglobata. Also other types of acne are classified based on their triggers such as acne rosacea - a diet induced form, chloracne due to overexposure to chlorinated compounds, acne associated with polycystic ovary syndrome, infantile acne, acne inversa, and drug-induced acne.^{5,6} Though the infection is not life threatening, it can lead to severe emotional distress among patients particularly in adolescents.

Considered the most common skin disorder, acne vulgaris (acne) can be a challenging condition to treat. Topical antibiotics have been widely used in the past, which resulted in the development of bacterial resistance, and thus these agents generally should be used for only short periods or in combination with retinoids, benzoyl peroxide or azelaic acid.⁷

Light or Laser therapy, including blue light and red light therapy, have been shown to be effective in treating acne. Any Laser treatment is good therapy for patients who will not tolerate other treatment.

Factors Responsible for Acne Vulgaris

Acne vulgaris being a chronic skin disease involving blockage and/or inflammation of pilosebaceous unit presents a distinct pathophysiological mechanism and the associated sign and symptoms determine its severity of infection in patients. The significant pathogenic factors for acne has been identified as: abnormal keratinization,



excess sebum production, proliferation of *Propionibacterium acne* (*p.acne*) and inflammation.⁸

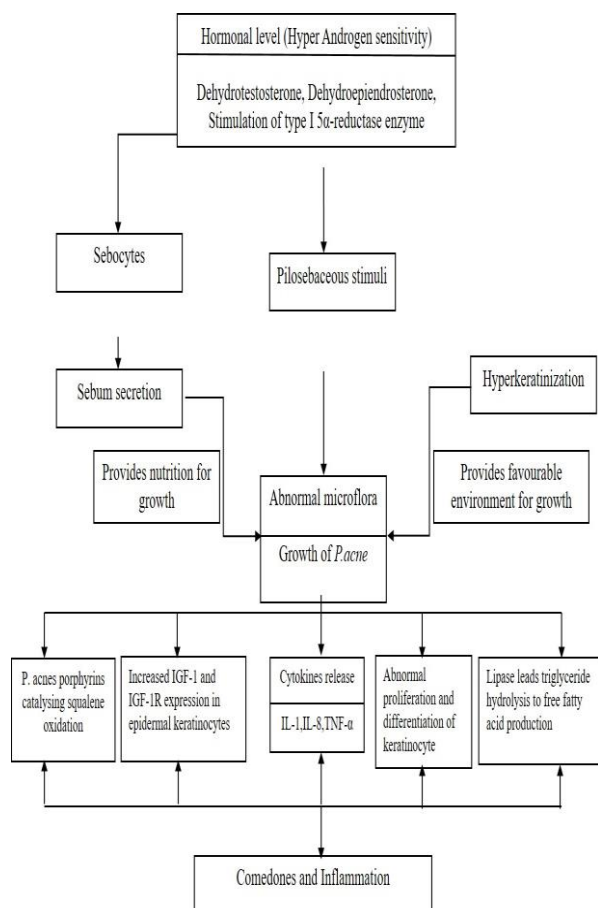


Figure 1: Pathogenesis of Acne

Abnormal Keratinization

Abnormal keratinization is the most crucial initial event in the development of acne lesions. The normal pattern of keratinization undergoes a gradual transition from the infundibulum to the acroinfundibulum. There are few number of filaments and desmosomes in acroinfundibulum than the infundibulum.⁹ Intracellular organelles are extruded into the extracellular space of the stratum corneum, where their lipid constituents form a lamellar structure that is involved in corneocyte cohesion and defective differentiation of keratinocyte leading to comedo formation due to high sebum secretion that in effect leads to interleukin 1 (IL 1) secretion and androgen release.¹⁰ Accumulation of abnormally desquamated corneocyte due to dilatation of sebaceous follicles lead to comedogenesis.¹¹ Hyper proliferative state of ductal keratinocytes may be induced by the modified lipid composition of the sebum.¹² Microcomedones and comedones show ductal hyperkeratinization and subsequent obstruction of sebaceous follicles.

High proliferative rate of ductal keratinization is believed due to the modified lipid composition of the sebum.¹³ Several researches have shown that hyper proliferation of keratinocyte could be due to hypersecretion of lipids like N-acylated forms of sphingolipids, such as ceramides,

promotes keratinocyte differentiation and sphingosine and sphingosylphosphorylcholine have been demonstrated to promote keratinocyte proliferation.¹⁴ Cytokines are also one of the factor that induce proliferation of keratinocytes and experimentally it was found that interleukin (IL) 1α induces comedogenesis.¹⁵

Increased Sebum Production

Pilosebaceous units involving follicles that produce small hairs but associated with large sebaceous glands are called “sebaceous follicles” and whenever sebaceous follicles are affected acne occurs. Sebum generally composed of triglycerides, free fatty acids (FFAs), wax esters, squalene, cholesterol esters and cholesterol.¹⁶ Bacterial lipases result in the formation of monoglycerides and diglycerides, as well as FFAs within the sebaceous follicle duct. The lipid found on the skin surface is the admixture of the pure sebum and epidermally derived lipids. The hydrolysis of triglycerides by *propionibacterium acne* yields FFAs which plays critical role in the inflammation by damaging the follicular epithelium.¹⁷ Sebum lipids acts as a nutrients for *P.acne* bacteria because it provides anaerobic environment to the bacteria which is favorable for its growth. In acne patients as the amount of sebum secretion increases, there is a corresponding decrease in linoleic acid content of sebaceous gland wax esters, triglycerides and FFAs of skin surface lipids. In this hypothesis linoleic acid is important content and its decrease leads to deficiency in follicular epithelium content leading to comedogenesis.¹⁸

Proliferation of *propionibacterium acne*

P.acne produces lipases which hydrolyze triglycerides, thereby releasing FFAs. FFAs can sufficiently irritate the follicular epithelium to result in its breakage and can thereby enable fatty acids to penetrate the dermis and cause inflammation. *P.acne* has been shown to increase the production of IGF-1 by keratinocytes and it activates IGF-1R, mostly located in the basal layer of the epidermis and also induced by *P. acne*, leading to proliferation of the keratinocytes and an increase in filaggrin expression through a paracrine pathway. This can potentially be another mechanism by which *P. acne* can potentiate comedogenesis.¹⁹

Hormonal Influences

Androgen plays an important role in acne pathogenesis and it controls the secretory activity of the sebaceous gland. The main influence of androgen on acne pathogenesis concerns the proliferation/differentiation of sebocytes and infundibular keratinocytes. The stimulatory effect of testosterone and 5α-dihydrotestosterone (DHT) on sebocyte proliferation was observed in primary culture of human sebocyte and hamster sebaceous gland cells.²⁰ Formation of microcomedones is caused by hyperkeratinization of the infundibulum of the follicular canal. It remains to be determined yet whether the higher activity of the type I 5α-reductase detected in the follicular infundibulum

is related to the abnormal differentiation of keratinocytes. In SZ95 sebocytes, the combination of testosterone and linoleic acid exhibit a synergistic effect on sebaceous lipids.^{21,22} Hormonal imbalance is difficult to control and it is the primary influence that increases the sebaceous gland activity which leads to increase in the sebum level, providing anaerobic environment to the *P.acne*.

Inflammation

Inflammation in acne is apparently a two-stage process. Initially, lymphocytes and polymorphonuclear leukocytes are recruited into the follicular epithelium; if the epithelium is disrupted, intrafollicular material is extruded into the dermis, resulting in a variety of inflammatory processes.²³ The free fatty acid hypothesis is the first mechanism that provides explanation about the inflammatory acne. The hydrolysis of sebaceous triglycerides by *Propionibacterium acne* bacteria forms the FFAs. The FFAs irritate the follicular epithelium and damage it, so FFAs goes in to dermis and can cause the inflammation.

Cytokines

Cytokines are present in normal sebaceous glands, *P. acne* produces soluble factors that are able to activate immune cells with the consecutive secretion of various pro-inflammatory cytokines (IL-8, tumor necrosis factor, IL-6). In a stress condition the cytokines levels are significantly high. The treatment of cultured sebocytes with *P. acne* and LPS significantly up regulates the expression of proinflammatory cytokines. While LPS stimulated CXCL8, TNF- α and IL-1 α , *P. acne* stimulated CXCL8 and TNF- α .²⁴ Arachidonic acid and calcium ionophore enhances the level of IL-6 and IL-8, but that of IL-1 β and TNF- α was not affected. In *in-vivo* studies, IL-6 was not detected in sebaceous gland of healthy person is skin. The difference of cytokines production in normal skin and acne lesions are shown in **Table 1**.²⁵

Toll-Like Receptors (TLRs)

Toll-like receptors are transmembrane proteins that are crucial players in the innate immune response to microbial and other invaders. TLRs are mainly expressed on immune cells, such as monocytes, macrophages, dendritic cells and granulocytes.

TLR stimulation mimics the action of IL-1 α and promotes the production of proinflammatory cytokines, prostaglandins, leukotrienes (LT) and chemokines.²⁶ Intriguingly, selected IL-1 receptor associated kinases (IRAK-1, 2, M and 4) are bifunctional. They can be recruited to the TLR complex and thus mediate TLR signaling but can also be associated with protein partners involved in T and B-cell receptor-mediated signaling pathways and so can be critical mediators for both innate and adaptive immune responses.²⁷

Human monocytes induce cytokine synthesis through TLR2 by *P.acne*. It is suggested that, by using this

pathway, the innate immune system is able to recognize microbial components and then induce cytokine/chemokine synthesis in acne.^{28,29}

Role of Langerhans Cells

Langerhans cells are dendritic cells of the skin which are antigen presenting cells, they are present in all layers of the epidermis, but are most prominent in the stratum spinosum. They also occur in the papillary dermis, particularly around blood vessels, as well as in the mucosa of the mouth, foreskin and vagina.³⁰ Recent studies indicate that normal adult human contains 10-20 billion resident memory T-cells. Epidermal Langerhans cells selectively and specifically induce the memory T-cell activation. Majorly stimulation of epidermal antigen presenting cells activates regulatory T-cell and minor activation of memory T-cell. In the non-scarring patients following the large influx of the inflammatory cells in the early lesion, there is a migration of the Langerhans cells from the dermal and epidermal layer to the draining lymph nodes,³¹ whereas in scarring patients the immune response was higher in resolving lesions which support the initiation of inflammatory reaction leading to scar formation.³² Factors affecting the local inflammation induced by Langerhans cell which induce inflammation are shown in **Figure 2**.

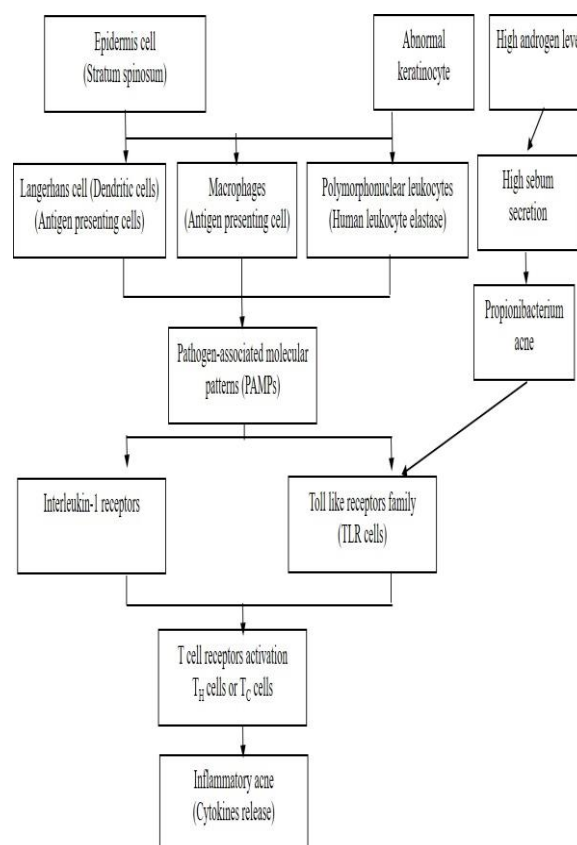


Figure 2: Factors Affecting Local Inflammation

Treatment of Acne Vulgaris

Several aspects have been used since the 2003 global alliance recommendations for acne management. These include the role of antibiotics in treatment, use of lasers

and light-based therapies, use of keratolytic agent.³³ There is an increased evidence supporting the recommendation of a combination of a topical retinoid plus an antimicrobial agent as first-line therapy for most of the patients with acne as a means of targeting multiple pathogenic features and both inflammatory and non-inflammatory acne lesions. Also using the retinoid oral therapy has more side effects and so is not preferred by physician for use as a sole treatment in severe forms of acne.

Topical Treatment

Effective management for acne should be directed at a combination of four factors which are associated with acne (**Figure 3**). A variety of therapies available with different anti-acne mechanisms. Topical therapies are preferred usually for patients with non-inflammatory or mild to moderate inflammatory acne. Topical agents minimize potential side effects associated with systemic agents. Topical agents include retinoid (keratolytic agent), Benzoyl peroxide (Anti-microbial agent), Anti-inflammatory agent, Antibiotics, and cleansing agents.

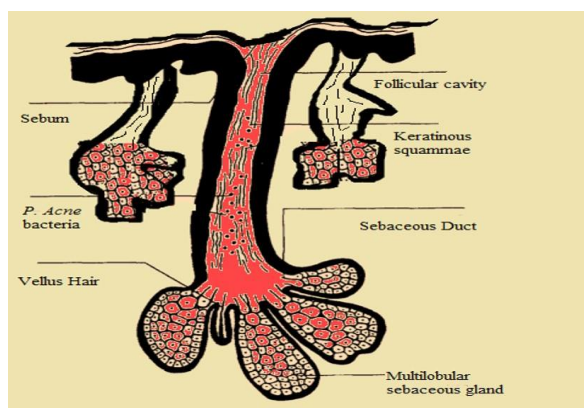


Figure 3: Physiological Sites for Treatment Strategies for Acne

Topical Antibiotics

Two topical antibiotics most useful to treat inflammatory acne are erythromycin and clindamycin. These agents reduce the population of *P.acne* on the skin surface and under the beneath of the skin. In addition to the anti-bacterial activity, antibiotics have anti-inflammatory activity and decrease the chemotactic agents and pro-inflammatory FFAs in the surface lipids. Clindamycin is the drug of choice for serious infections, with other antibiotics like tetracycline, erythromycin as alternatives in cases of allergy or with concern about resistance to single agent.³⁴

Retinoids (Tretinoin)

Historically, tretinoin (all-trans retinoic acid) has been used as a comedolytic agent to treat mild-to moderate acne.³⁵

Used as a stand-alone treatment or in combination with antibiotics, its ability to stimulate the growth of new cells, unclog pores, and promote the normal flow of sebum is

well-proven. However, over the years there has been a growing awareness within the professional community that tretinoin also possesses a broad range of modulating properties, which could play a beneficial role in the disruption of the immune-inflammatory cascade of acne vulgaris and the proinflammatory factors associated with it.³⁶ Cytokines are transient immunomodulating substances secreted by specific cells of the immune system. Capable of carrying messages between local cells via signaling pathways, they regulate the duration and amplitude of the immune response.³⁷ Several studies have shown that tretinoin is a potent inhibitor of TNF- α production and reduce the inflammatory cytokines. The first study evaluated the effects of tretinoin on the release of TNF- α in CD14+ human monocytes, wherein heat-killed *P. acne* served as the antigenic stimulant. Results showed that tretinoin was able to down regulate the induction of TNF- α by 70%.³⁸ In a second study, investigators evaluated the effects of tretinoin on the production of TNF- α secretion by human keratinocytes activated with lipopolysaccharides and IFN- γ . Tretinoin inhibited the release of TNF- α up to 60 percent in a dose dependent fashion.³⁹ Another similar investigation measured the inhibitory effect of tretinoin on TNF- α release by human keratinocytes. Immunoglobulin E was used as the induction agent to stimulate the release of TNF- α . Results showed a time- and dose-dependent inhibition effect, with the greatest level of TNF- α inhibition being approximately 70%.⁴⁰

To enhance compliance and avoid complications with tretinoin, patients should be informed of its potential side effects, which include desquamation, burning, erythema, and an exacerbation of inflammatory acne lesions ("pustular flare"). The irritation, which is usually transient, can be minimized by selection of an appropriate starting dose, applying tretinoin to dry skin, and gradually increasing the concentration. To avoid the complications with tretinoin the mildest concentration (0.025%) is prescribed first and then the higher concentrations preferred (0.01%). This allows the patient to adjust gradually to the therapy while maintaining its efficacy.

Benzoyl Peroxide

Benzoyl peroxide rapidly improves both inflammatory and non-inflammatory lesions; it can therefore be used alone for the treatment of mild acne. But for severe inflammatory acne it is not effective as a single agent but should be used in combination with keratolytic agent. It is available in concentrations ranging from 2.5% to 10% and in formulations that including gels, creams, lotions, and washes.

Benzoyl peroxide can initially irritates the skin and rarely elicit an allergic contact dermatitis. As with tretinoin, accommodation to the drug can be achieved by gradually increasing the frequency of application and initiating with the lowest concentration available as the case with Isotretinoin, for containing the lesions.⁴¹

Combination Therapy

Tretinoin increases the penetration of other topical agents used in conjunction with it. The efficacy of topical antimicrobials can therefore be enhanced with this combination. Tretinoin reduces hyperkeratosis, thereby diminishing anaerobic conditions in the follicle. Topical antibiotic (clindamycin) and benzoyl peroxide further inhibit *P. acne*, neutrophil chemotaxis, and the production of FFAs. The concomitant use of tretinoin and an antimicrobial agent can therefore decrease keratinization, *P.acne* and inflammation, thus addressing three of the pathogenic factors implicated for acne. It is also better tolerated, because the irritant effects of tretinoin are decreased with the addition of clindamycin. A reduction in lesion count and irritation is also seen when clindamycin is combined with benzoyl peroxide.⁴²

Benzoyl peroxide and tretinoin have synergistic effect and additive effect also tretinoin and topical erythromycin is also more effective in combination than either monotherapy. Another newly approved formulation is dapsone gel. Oral dapsone is a sulfone with antimicrobial and anti-inflammatory properties and a topical formulation has been found to help particularly with inflammatory acne lesions.⁴³ This may be an alternative to topical antibiotic therapies, for which there is growing bacterial resistance.

Other Topical Treatment

Dapsone is one of the useful ingredient for topical action as an anti-microbial agent. Salicylic acid is comedolytic agent accelerates the resolution of inflammatory lesions. Salicylic acid is less effective than retinoids but may be useful in combination also as a liquid cleanser or along with topical antioxidants to improve skin texture and to prevent skin from further damage.

Also customized topical skin care treatment plan including cleansers and crèmes can be undertaken for the most advanced and effective therapy employing a combination of prescription and non-prescription treatments.

Systemic Therapy

Systemic therapy is valuable for moderate to severe inflammatory acne, but in combination with topical therapy is more useful so as to minimize the side effects of systemic therapy. Most useful ingredients for systemic delivery are antibiotics, isotretinoin, hormonal, or combination of them.

Oral Antibiotics

The most useful oral antibiotics includes tetracycline, erythromycin, azithromycin, doxycycline, minocycline, dapsone, and sulfamethoxazole-trimethoprim. They suppress systemic inflammatory mediators and *P.acne* also decrease the FFAs in surface lipids.

Tetracycline is the most useful antibiotics and is beneficial in moderate inflammatory acne but recent studies

showed that tetracycline can associated with hepatotoxicity with prolonged use.⁴⁴ The potential side effects of tetracycline include modification of gastrointestinal and mucosal flora leading to vaginal candidiasis and gastrointestinal upset. Oral erythromycin also reduces papules and pustules by decreasing *P. acne* and by an anti-inflammatory effect. Although *P. acne* tends to develop resistance for all antibiotics the relative propensity differs, by which the resistance to both clindamycin and erythromycin is more than that exhibited towards tetracycline.⁴⁵ Its use is also often limited by gastrointestinal side effects.

Erythromycin is a good alternative for patients who are photosensitive. Minocycline is a potent antibacterial agent that has the ability to penetrate into the sebaceous gland; its higher concentration in the follicle effectively inhibits the growth of *P.acne*. Although it is costlier, minocycline is less likely to cause GI upset and phototoxic reactions. Vertigo like symptoms can sometimes be avoided by gradually increasing the dose of the drug. Doxycycline, although also effective for treating acne, can be more photosensitizing.⁴⁶ When the aforementioned antibiotics are not effective, treatment with trimethoprim-sulfamethoxazole can be attempted.⁴⁷ Because it is lipid soluble, it is effective for severe acne and gram-negative folliculitis (which should always be considered in the nonresponsive patient with papulopustular involvement). This agent, however, has the potential for severe, although rare, reactions, including drug eruptions (rarely toxic epidermal necrolysis) and bone marrow suppression.⁴⁸ Resistance to *P. acne* should be considered in patients whose response decreases to therapy that was previously successful. An alternative should then be substituted.

Isotretinoin

Isotretinoin (13-cis retinoic acid) is indicated for patients with nodulocystic acne and for those with severe inflammatory disease in whom treatment has failed with the aforementioned combinations.⁴⁹ None of the former antibiotics and other ingredients are effective in suppressing the sebum production. Isotretinoin is the only drug that directly influences abnormal keratinization and blocks sebum secretion by inhibiting sebaceous gland activity.²⁷ **Table 2** lists a summary of the side effects observed and their severity during use of various anti-acne agents for treatment.

Advances in Treatment of Acne Vulgaris

From the pathophysiological evidence for the cause of acne vulgaris it is now well understood that the inflammatory mediators are most critical targets to control at lesioned site and therapy should be designed that controls the pro-inflammatory and inflammatory mediators or emerging with strategies that act locally on sites.

As described earlier, of the various treatment strategies used for treatment of acne some have potential side



effects limiting their chronic use in disease condition and success of therapeutic intervention varies largely. However, advancements in field of modern therapeutics have led to the emergence of strategies and technologies that can be customized as per severity of the infection by employing newer generations of medicaments for skin care and treatments, and employing non-invasive procedures for achieving superior outcomes from the treatment within relatively short span of therapeutic regime and time for treatment.

Photodynamic therapy since now has been widely used therapeutic strategy in cancer treatment as it is less invasive than surgery and with targeting capabilities to specific site. PDT involves the mediation of molecular damage on the cancer cells leading to their necrosis and apoptosis by employment of light absorbing drugs. Such photosensitive drugs generate reactive oxygen species *in situ* under the influence of light thus mediating their cytotoxic effects.⁵⁰ *P. acne*, the primary organism implicated in acne, produces endogenous chromophores called porphyrins. The cellular machinery involving the production of porphyrins during metabolism by *P. acne* provided the basis for employing light for inactivation of bacteria under the skin.^{51,52} Use of light at a specific wavelength leads to predisposition of hematoporphyrin group to oxidative degradation leading to generation of reactive oxygen species (ROS) and singlet oxygen radicals. Various photosensitizers that have been used so far includes protoporphyrin IX, Methylene blue, indocyanine green, indole-3- acetic acid etc. each being employed based on the wavelength of light to be utilized.⁵³ One of the widely used photosensitive agent is amino levulinic acid (ALA, 5-amino-4-oxopentanoic acid), an amino-acid molecule and an essential precursor in hemoglobin biosynthesis carried out by a wide range of both eukaryotic and prokaryotic cell types. It is taken up inside pilosebaceous unit where it gets converted to a photosensitive protoporphyrin IX (PPIX), leading to excess of porphyrin in and around the infection site and subsequently form singlet oxygen under influence of light leading to cytotoxicity to the bacterial cell. ALA thus destructs the bacterium by interfering in the heme biosynthetic pathway.^{54,55} The light used for activation can range from blue to red light depending on the type of photosensitizing agent employed having different wavelength maxima for their photosensitization. This mediates bacterial killing of *P. acne* and clears the cutaneous lesions with little damage to the adjacent skin. This method can be used in patients suffering from moderate to severe forms of cystic acne. The treatment also aids in unclogging the pores, shrink oil glands and shutting down the turn over from sebaceous glands thus help prevent scar formation.

Reactive oxygen species (ROS) are short lived molecular structures that are generated at low level during aerobic metabolism. Keratinocytes have capacity to produce ROS upon exposure to toxic compounds and ultraviolet radiation that depends on the differentiation capacity of

the cells.^{56,57} ROS are involved in acne pathogenesis by lipid peroxidation of the epithelium. When antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), and glucose-6-phosphate dehydrogenase (G6PD)) are less in content then ROS level increases. When these enzymes are less in amount ROS starts lipid peroxidation.^{58,59} These enzymes have been studied in erythrocytes different from those used in previous studies.⁶⁰ The ROS produced by *P. acne*-stimulated keratinocytes lead to the lysis of keratinocytes and limit *P. acne* growth. Lipid peroxidation of follicular epithelium leads to breakage and leakage of the content finally initiate inflammatory reactions.

A study was carried out to determine the effect of use of photodynamic therapy (PDT) with 20% 5-aminolevulinic acid (ALA) and Methyl amino-levulinate as photosensitizing agents for the treating of mild to severe acne vulgaris. The study involved use of advanced fluorescent technology with use of a pulsed light source of 420-950 nm for photo-activation of ALA. It was concluded that ALA PDT was more effective against inflammatory and cystic acne than comedonal acne with a total reduction of 50 % in inflammatory lesion counts at the end of the treatment.⁶¹

One of the major side effects for the treatment is the pain associated during the therapy and need for repeated exposure in course of treatment which limits the patient compliance. The exact mechanism of pain production is not yet clear, yet the extent of pain sensation can be decreased by exposing a limited area of skin during treatment.

Use of Laser in acne for resurfacing of damaged or scarred skin can also help eliminate acne scars and acne skin damage and reveal the smooth, fresh skin underneath. The highly intense and directional beam of laser is used for targeting a small area of tissue on skin thus giving the advantage to the procedure for the removal of scars in a precise, rapid, bloodless fashion achieving excellent results within a short treatment time of few weeks. The lasers used in acne and their characteristics are listed in **Table 3**.

Lasers are noninvasive and efficacious options that do not require daily dosing and improve patient compliance. The cost, potential discomfort, requirement of physician and need for an office-based procedure, however, may limit their use. They typically require multiple sessions to achieve the desired results. With additional clinical trials underway, laser treatment of acne can potentially be preferred alternative to the current therapies.

Improvement in acne lesions has also been observed by employing microcrystals for removal of damaged skin cells known as Microdermabrasion.⁶⁷ It is a gentle procedure with progressive treatment schedule, but has to be done over a long period of time.⁶

The combined use of platelet-rich plasma (PRP) with skin needling in acne has also shown efficacious results. The concentrated form of Plasma in platelet-rich plasma (PRP)



contains autologous growth factors, especially epidermal growth factor, platelet-derived growth factor, transforming growth factor β and vascular endothelial growth factor, that act synergistically with growth factors induced by skin needling in order to enhance the wound-healing response and tissue repair during treatment of scars.⁶⁸ This approach has been evaluated as superior than by use of PRP or micro-needling or trichloroacetic acid alone⁶⁹ or combination of micro-needling with Vitamin C.⁷⁰

Palliative treatment measures for acne scar and maintaining good skin health includes use of facial fillers such as restylane and is to be injected into the area of the scar thus smoothing depressions. Various types and concentrates of chemical peels, consisting of a chemical solution to remove the fine outer layers of the skin can also be used for achieving smoother skin. However, application period is desired for weeks before complete smoothing is observed. Use of medical facials can soften and loosen dead skin cells and treat oily, dry, dehydrated, acne and acne prone skin conditions by combining deep steam cleaning and extractions properties to achieve deep cleansing and exfoliation.

Other Treatment Measures for Acne Scar

Immune response against the bacteria or foreign material is the host defense mechanism but due to aggravation of immune response of the host against pathogen will create the inflammation.

Inflammatory reactions lead to pus formation due to host defense mechanism and that may lead to white or black head that contains dead cells, dead leukocytes and blood which gets/needs to be cleared from the skin.

If the pus formed does not get excluded, it causes scar formation and also may aggravates the inflammation.

Peeling out the pus before maturation causes the aggravation of the inflammation and infect the other cells near to lesioned area forming the scar but after complete

maturation of comedone it should be expelled out from the skin.

The researches have demonstrated increased susceptibility to acne infection in the population consuming dairy products derived from bovine source which leads to increase in glycemic index along with its hormonal components such as reduced steroids, albumin, 5 α -pregnandione etc. which serves as a stimulant in the etiology of inflammatory reactions leading to aggravation of symptoms.^{71,72} The role of omega fatty acids is also important as it regulates the levels of IGF-1 which is involved in the sebaceous follicle hyperkeratinization. The favored ones are the food containing omega 3 fatty acids.⁷³ Some extracts from the plant e.g *G.glabra* and *P.lactiflora* have been evaluated to have modulatory effect on testosterone levels.⁷⁴ The role of salts has also been reported in the literature which suggest its therapeutic potential in downregulating inflammatory mechanism. Magnesium has reversible anti-inflammatory effect, reduces the cytokine production and I κ B α gene expression. MgSO₄ down regulates cytokine production in an NF- κ B dependent manner which is a central regulator of inflammation-induced cytokine production. Magnesium is second most abundant cation in the body it plays control role in enzyme activation or inhibition, and regulatory roles by modulating cell proliferation, cell cycle progression and differentiation. Even though less under-magnesium has great connection with immune system. magnesium play as a co-factor for immunoglobulin synthesis, C'3 convertase, immune cell adherence, antibody-dependent cytotoxicity, IgM lymphocyte binding, macrophage response to lymphokines and T helper-B cell adherence.⁷⁵

MgSO₄ supplementation reduces the percentage of monocytes producing TNF- α and IL-6.⁷⁶ All these treatment alternatives offer renewed strategies to be explored for the management of acne and can be used in addition to the primarily used agents for achieving complete remission of the lesion in acne vulgaris.

Table 1: Current aspects of cytokine production in normal skin, acne lesions and associated factor*. (Reprinted with permission)

S. No.	Condition	IL-1 α	IL-6	IL-8	CXCL8	TNF- α
1.	Normal person, healthy skin		-	++		
2.	Acne patient, uninvolved skin		+	++		
3.	Acne patient, involved skin		++	+++		
4.	<i>Propionibacterium acne</i> stimulation	No effect			↑	↑
5.	LPS treatment	↑			↑	↑
6.	Increased PAF-R expression			↑		
7.	ectopeptidase	↑				
8.	CRH		↑	↑		
9.	α -MSH			↓		

↑= Increase level, ↓= Decrease level, += Mild, ++= Moderate, +++= Extreme

IL, interleukin; TNF, tumor necrosis factor; LPS, lipopolysaccharide; PAF-R, platelet-activating factor receptor; CRH, corticotropin



releasing hormone; α -MSH, α -melanocyte stimulating hormone. 11L-1 receptor antagonist is significantly upregulated in cultured sebocytes in the presence of dipeptidyl peptidase IV and aminopeptidase N inhibitors.

Table 2: Side Effects of Different Anti-acne Agents

Ingredients	Superficial Redness	Dryness	Itching	Scaling	Burning	Nausea and Vomiting	Skin Redness
Tretinoin	+++	+++	++	+++	+	-	++
Clindamycin	++	-	+++	-	+	++	++
Isotretinoin	+++	+++	+	++	+	-	++
Benzoyl peroxide	+	++	+	++	+	-	++
Topical Antibiotics	-	-	+	+	-	-	-
Adapalene	+	+	+	+	++	-	+
Tazarotene	+	+	+	+	+	-	+++
Azelaic acid	+	+++	+++	+	++	-	+++

+++ = Severe; ++ = moderate; + = Weak; - = none

Note: A change in frequency of application will reduce some of the side effects.

Table 3: Laser Therapy in Acne

Laser	Characteristics	Use	Side Effects	Ref.
Potassium titanyl phosphate laser (532 nm)	Produce beam in green visible spectrum. Chromophores targeted are melanin, oxyhaemoglobin and red tattoo pigment.	For vascular lesions like facial and leg telangiectasias, In pigmented and non-vascular skin lesion, tattoos and rosacea.	Low side effect profile – mainly pain, and rarely redness and swelling, bruising, scarring and skin dyspigmentation.	62
Diode laser (1450 nm)	Works using IR spectrum. Approved for acne by FDA with a dynamic cooling device - preserve the epidermis while causing thermal damage to the sebaceous glands, which may temporarily arrest their sebaceous output.	Facial rejuvenation. Improves facial and periorbital rhytides. Remodels and promotes collagen formation within the skin.	Postoperative erythema, edema, and hyperpigmentation in patients with darker skin types.	63 64
Erbium:glass laser (1540 nm)	Operates in mid-IR range. Reach a depth of 0.4 to 2 mm and targets intracellular water.	Treatment of rhytides.	No side effects.	65
Pulsed dye laser (585 nm)	A beam of visible coherent yellow light from laser, targets oxyhemoglobin in microvessels.	Treat Cutaneous vascular lesions such as hemangiomas, port-wine stains, and facial telangiectasias.	Discomfort during administration, postoperative purpura and even skin discoloration or dyspigmentation.	66

CONCLUSION

The treatment strategies for Acne vulgaris have gradually advanced from the times which involves the use of topical antibiotics, retinoids, benzoyl peroxide or a combination of above for mild to moderate infections while use of systemically administered medication for moderate to severe cases of acne which takes time for healing as well as possibility of scar formation, to the use of radiological and surgical procedures for achieving accelerated tissue

repair and minimal invasion to healthy tissues for treatment of acne. Use of combination of medication therapy for maintenance and remission is favorable along with the use of surgical procedure for achieving immediate effects in severe cases. Though the wide applicability of such procedures is still awaited due to the use of sophisticated instrument requirement and is also dependent on skill of the medical practitioner, they are gaining increased attention of researchers for



amalgamating the use of technology and science for betterment of individual health.

Several researches are being carried out to exactly determine the benefits, ease of use and affirm the therapeutic effects of such advanced treatment strategies and increasing the clinical applicability and widespread use of such strategies.

Advanced treatment alternatives for treatment of acne vulgaris can thus holds the key for achieving quick effects and added benefits can be achieved by combined use of therapeutic and technological advancements.

Conflict of Interest

The authors confirm that this article or its content has no conflicts of interest.

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